National Cancer Institute

Demystifying Cancer Screening: Science versus Intuition

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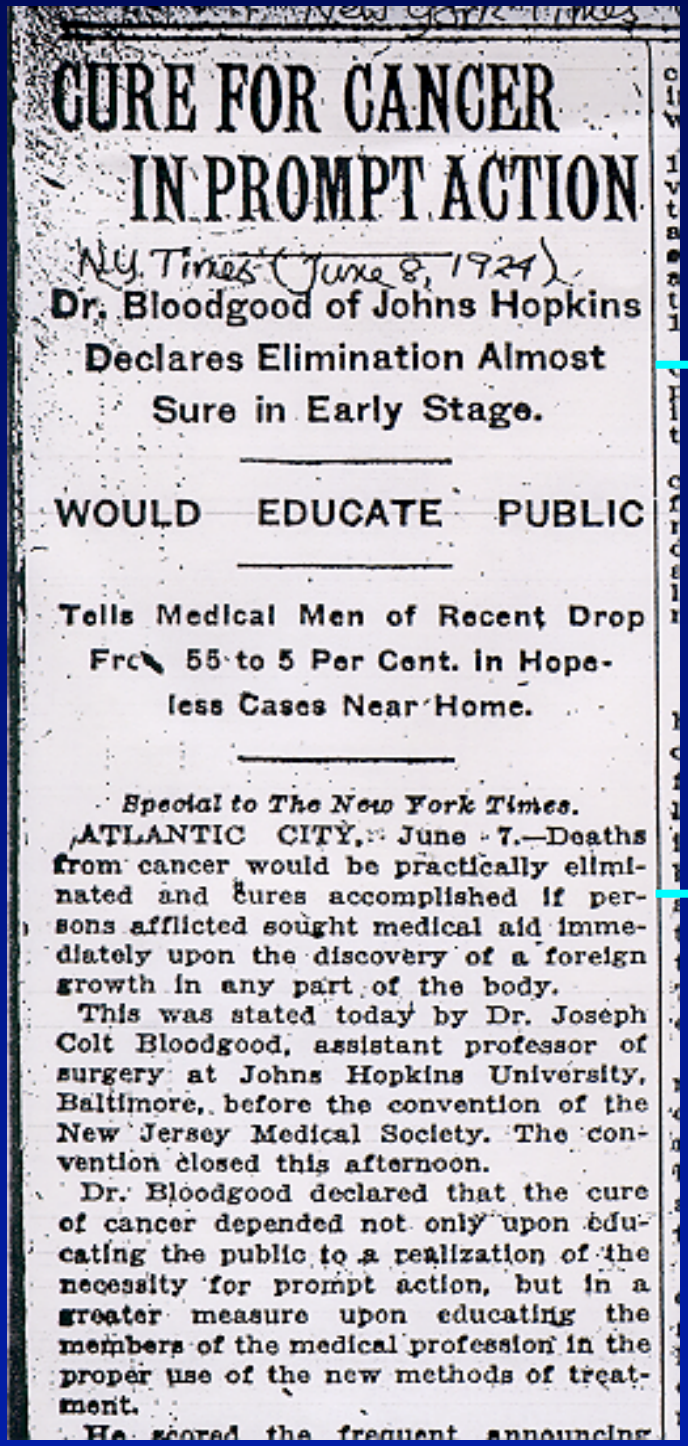
Division of Cancer Prevention)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

In the field of cancer screening,
" It is particularly important to be able to sort out what is known versus what makes sense…."

Daniel Wolpaw
Medical Clinics of North America, 1996

Nearly a Century of Enthusiasm for Cancer Screening



CURE FOR CANCER IN PROMPT ACTION

N.Y. Times (June 8, 1924)

Dr. Bloodgood of Johns Hopkins Declares Elimination Almost Sure in Early Stage.

WOULD EDUCATE PUBLIC

Tells Medical Men of Recent Drop From 55 to 5 Per Cent. in Hopeless Cases Near Home.

Special to The New York Times.

ATLANTIC CITY, June 7.—Deaths from cancer would be practically eliminated and cures accomplished if persons afflicted sought medical aid immediately upon the discovery of a foreign growth in any part of the body.

This was stated today by Dr. Joseph Colt Bloodgood, assistant professor of surgery at Johns Hopkins University, Baltimore, before the convention of the New Jersey Medical Society. The convention closed this afternoon.

Dr. Bloodgood declared that the cure of cancer depended not only upon educating the public to a realization of the necessity for prompt action, but in a greater measure upon educating the members of the medical profession in the proper use of the new methods of treatment.

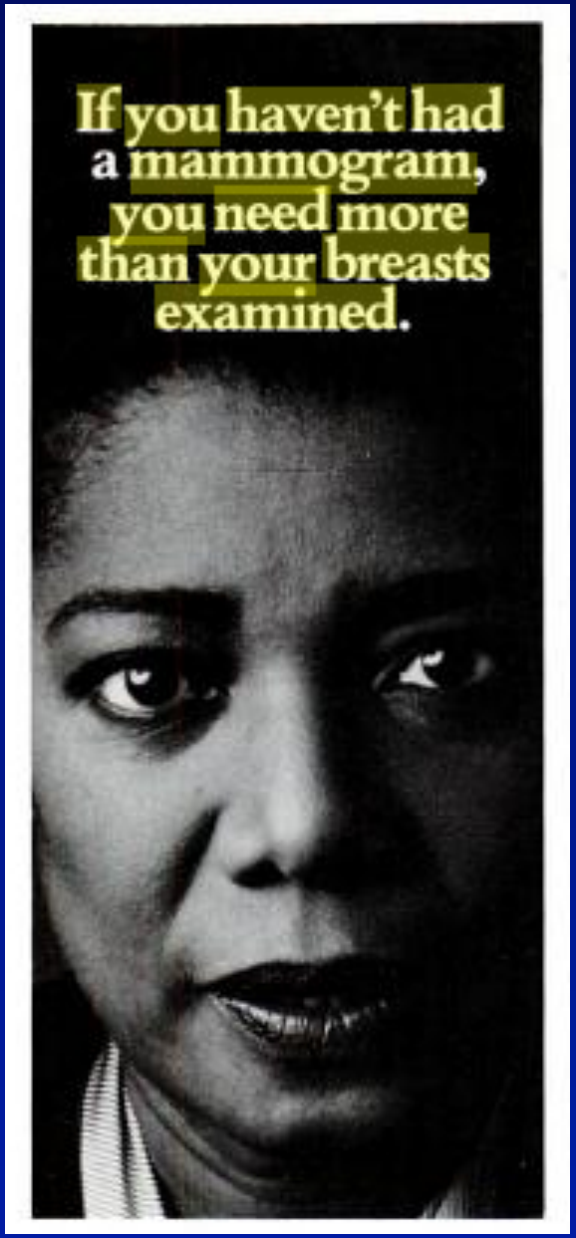
He scored the frequent announcing

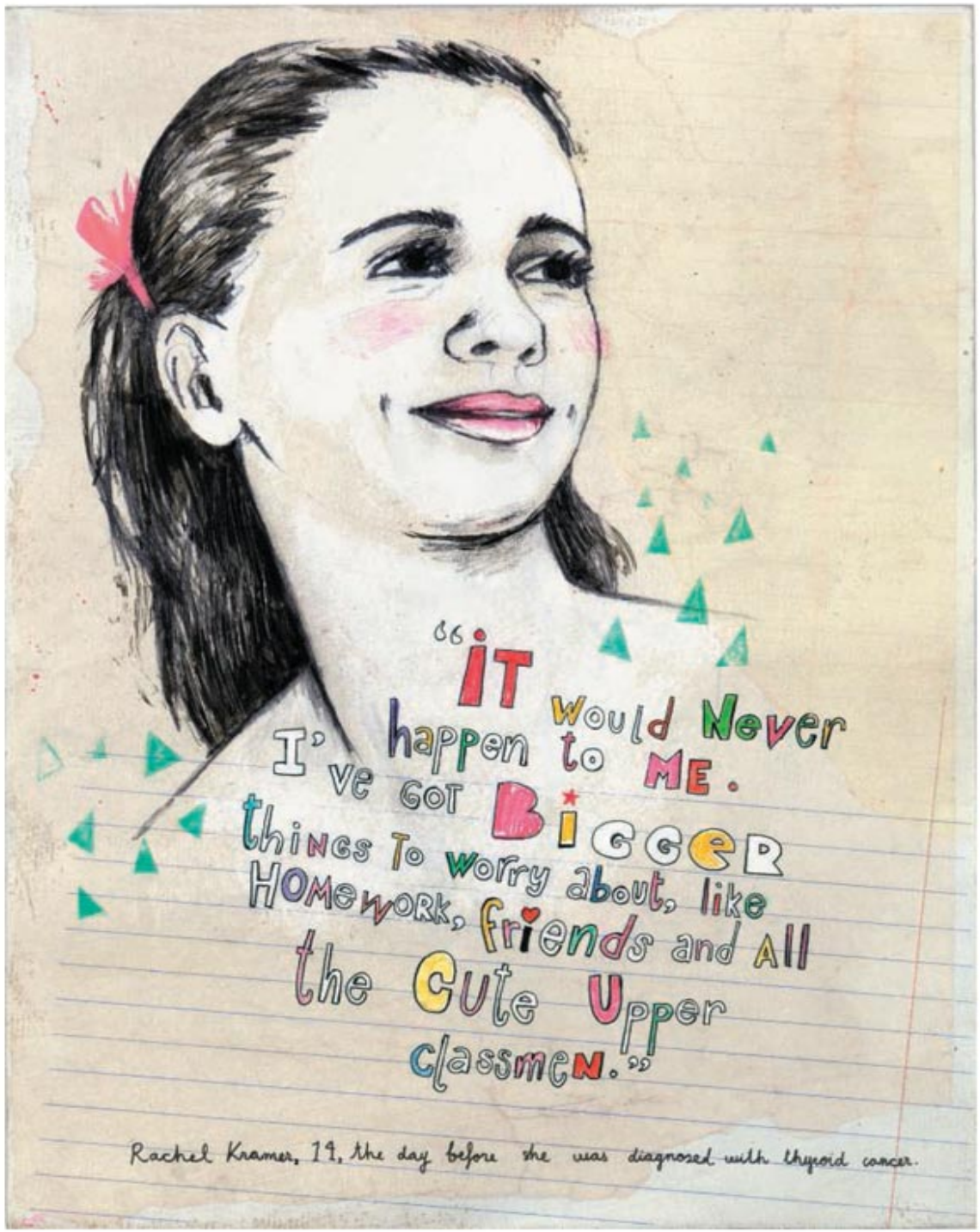
"Dr. Bloodgood of Johns Hopkins declares elimination [of cancer] almost sure in early stage."

"Deaths from cancer would be practically eliminated…if persons afflicted sought medical aid immediately upon the discovery of a foreign growth in any part of the body."


Prostate
Cancer
Awareness
USA 33
Annual
Checkups
and
Tests
© USPS 1998
PRELIMINARY DESIGN


If you haven't had a mammogram, you need more than your breasts examined.
A mammogram is a safe, low-dose X-ray that can detect breast cancer before there's a lump. In other words, it could save your life and your breast.
If you're a woman over 35, be sure to schedule a mammogram. Unless you're still not convinced of its importance.
In which case, you may need more than your breasts examined.
Find the time.
Have a mammogram.
AMERICAN CANCER SOCIETY
Give yourself the chance of a lifetime.


If you haven't had a mammogram, you need more than your breasts examined.



Levels of Decision Making

Level I: *"Would you have this done for yourself or for someone else in your immediate family?"*

Influenced by one's personal experience with the disease and capacity to deal with risk.

Affects few people.

Level II: *"What would I recommend to my patient/client?"*

Physician making a recommendation for his/her patients. Influenced by prior experience, but the scientific evidence may play a greater role.

Affects possibly hundreds of people.

Level III: *"What would I recommend to the nation, the world?"*

Across-the-board recommendations for a population.

Must be based on rigorous assessment of the scientific evidence.

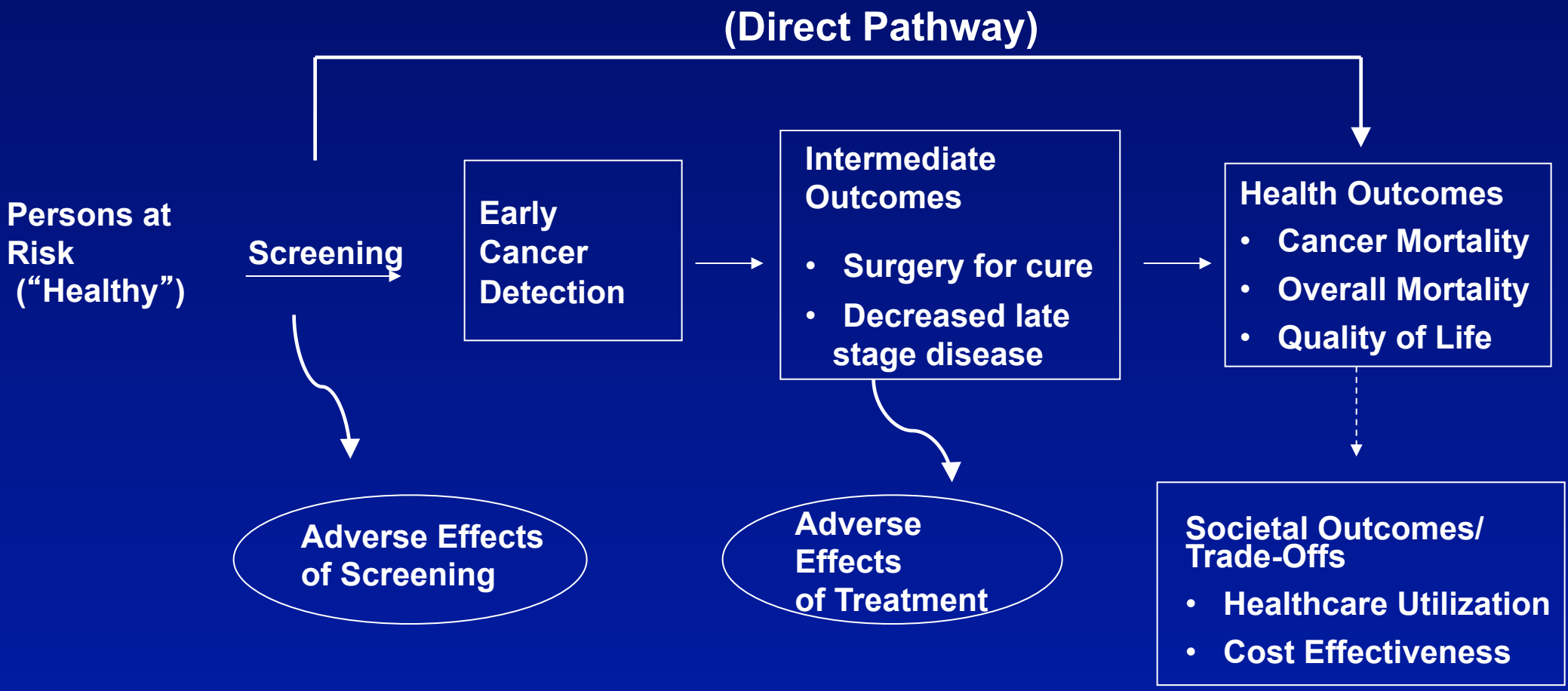
Affects hundreds of thousands, even millions of people.

slide courtesy of Leon Gordis, Ph.D., Johns Hopkins University

Core Issues in Screening and Prevention

- It is difficult to make healthy people better off than they already are.
- Strong evidence of benefit is important when putting large numbers of healthy people in harm's way.

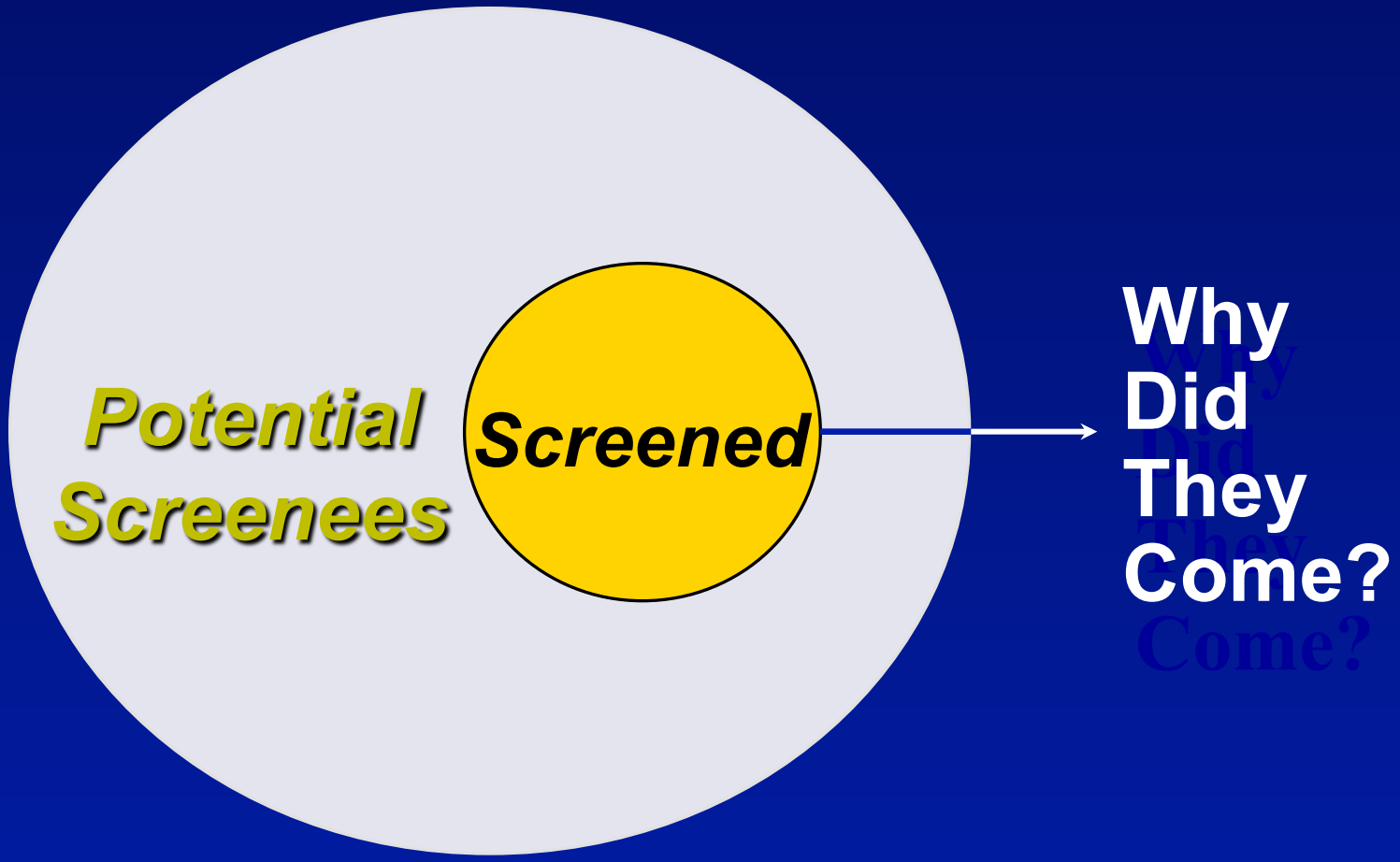
Analytic Framework for Cancer Screening



Potential Biases in Screening Studies

- Selection Bias
- Lead Time Bias
- Length Bias

Selection Bias



Healthy Volunteer Effect in the PLCO Trial

	PLCO Trial (%)		National Health Interview Survey (%)	
	Men	Women	Men	Women
Smoking status				
Current smoker	12	10	21	18
Regular physical activity	85	84	56	52
Education				
Less than high school	8	7	23	24
High school/post-high school	51	63	52	60
College degree	41	30	25	16
Medical diagnosis				
Cancer	2	7	8	10
Diabetes	9	7	14	13
CAHD, stroke	15	7	19	10
Hypertension	34	34	42	44

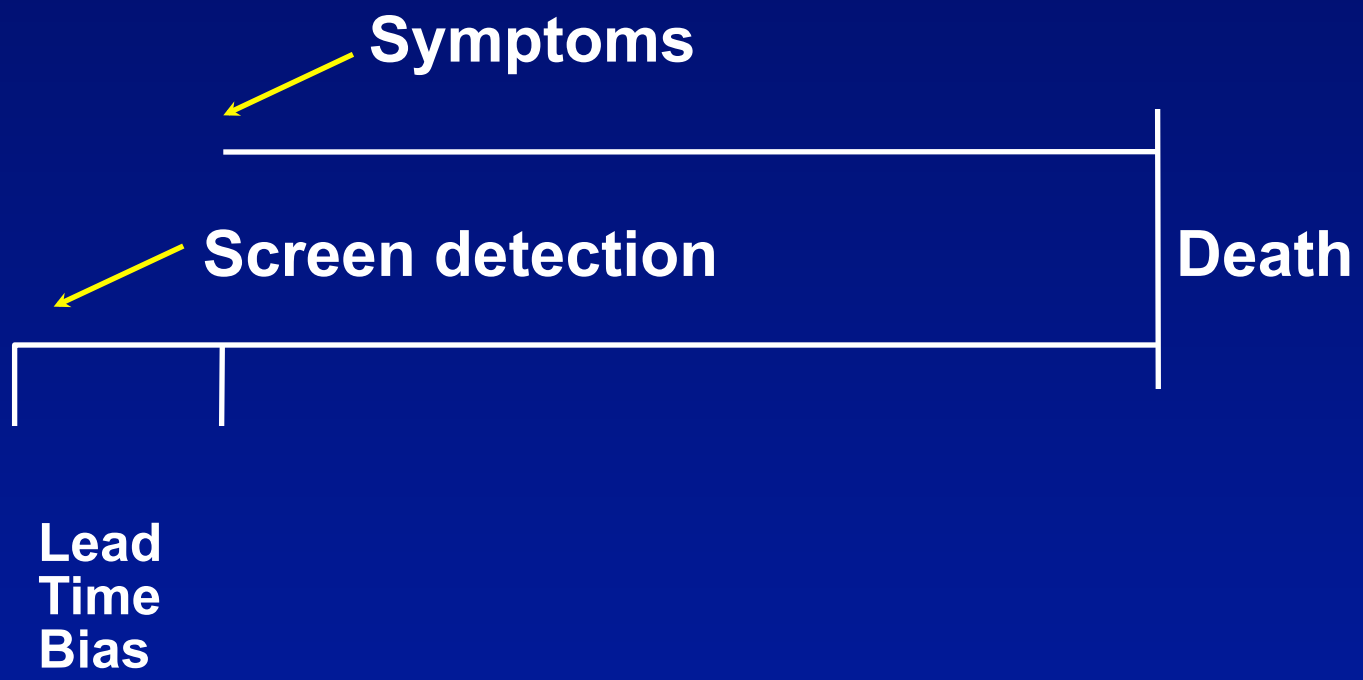
(P Pinsky, Am J Epi, 2007)

Standardized Mortality Ratio in PLCO Participants

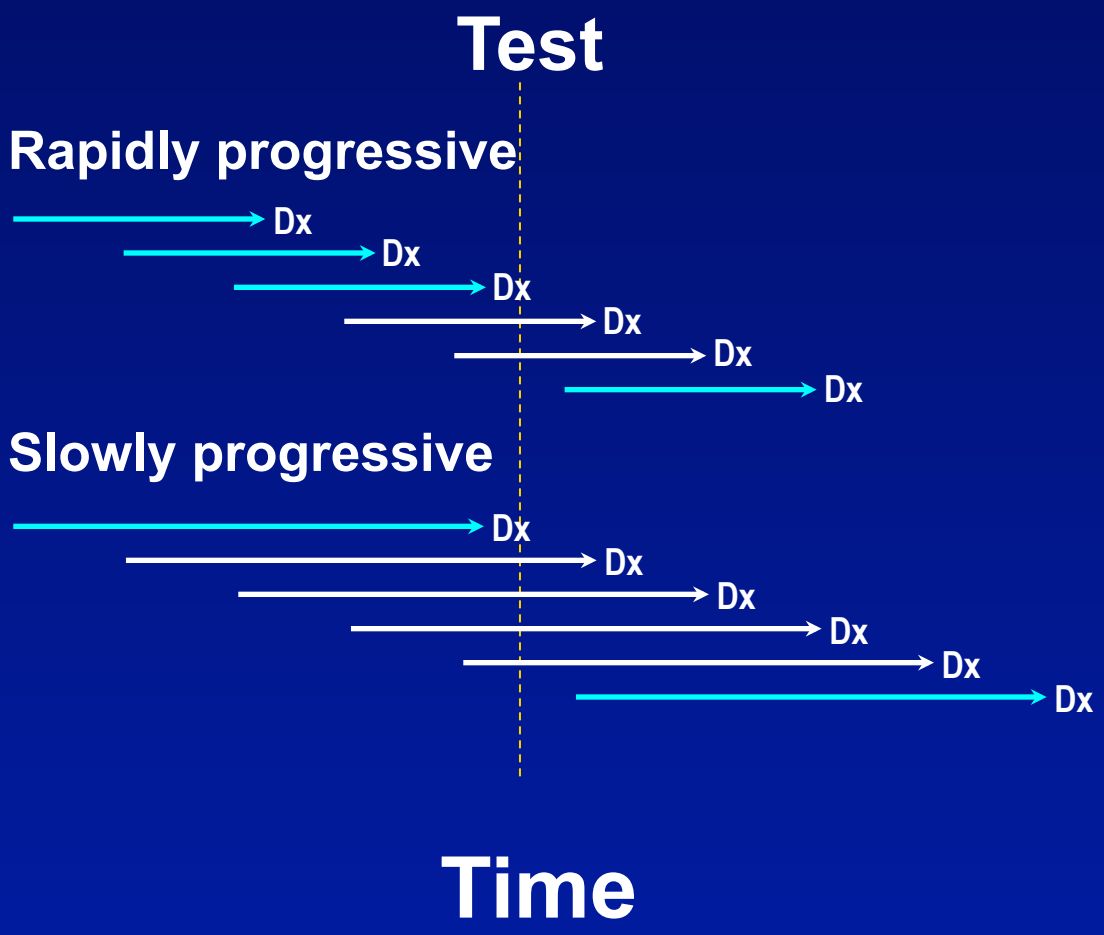
	Standardized mortality ratio (%)	95% confidence interval
All non-PLCO causes	43	42-44
Cardiovascular	37	35-38
Digestive	34	30-38
Respiratory	34	31-36
Diabetes	28	24-31
Injuries and poisoning	64	58-70
All non-prostate, lung, colorectal or ovarian cancers	56	54-59

(P Pinsky, Am J Epi, 2007)

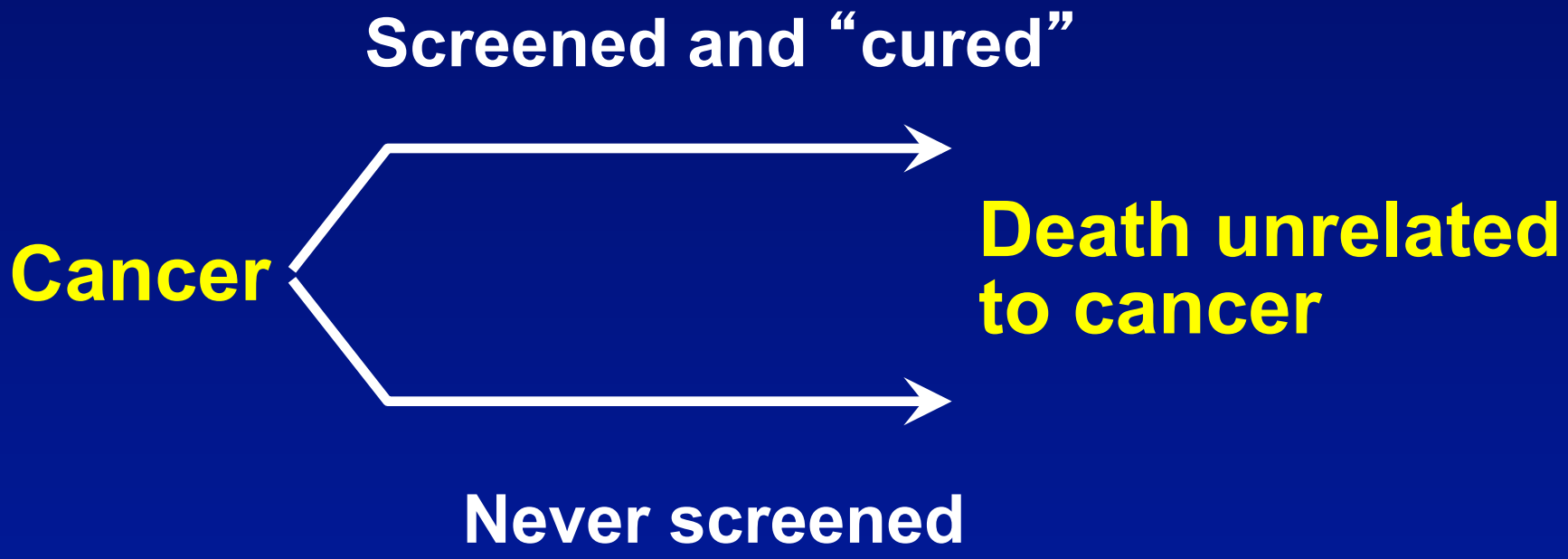
Lead Time Bias



Length Biased Sampling



Overdiagnosis

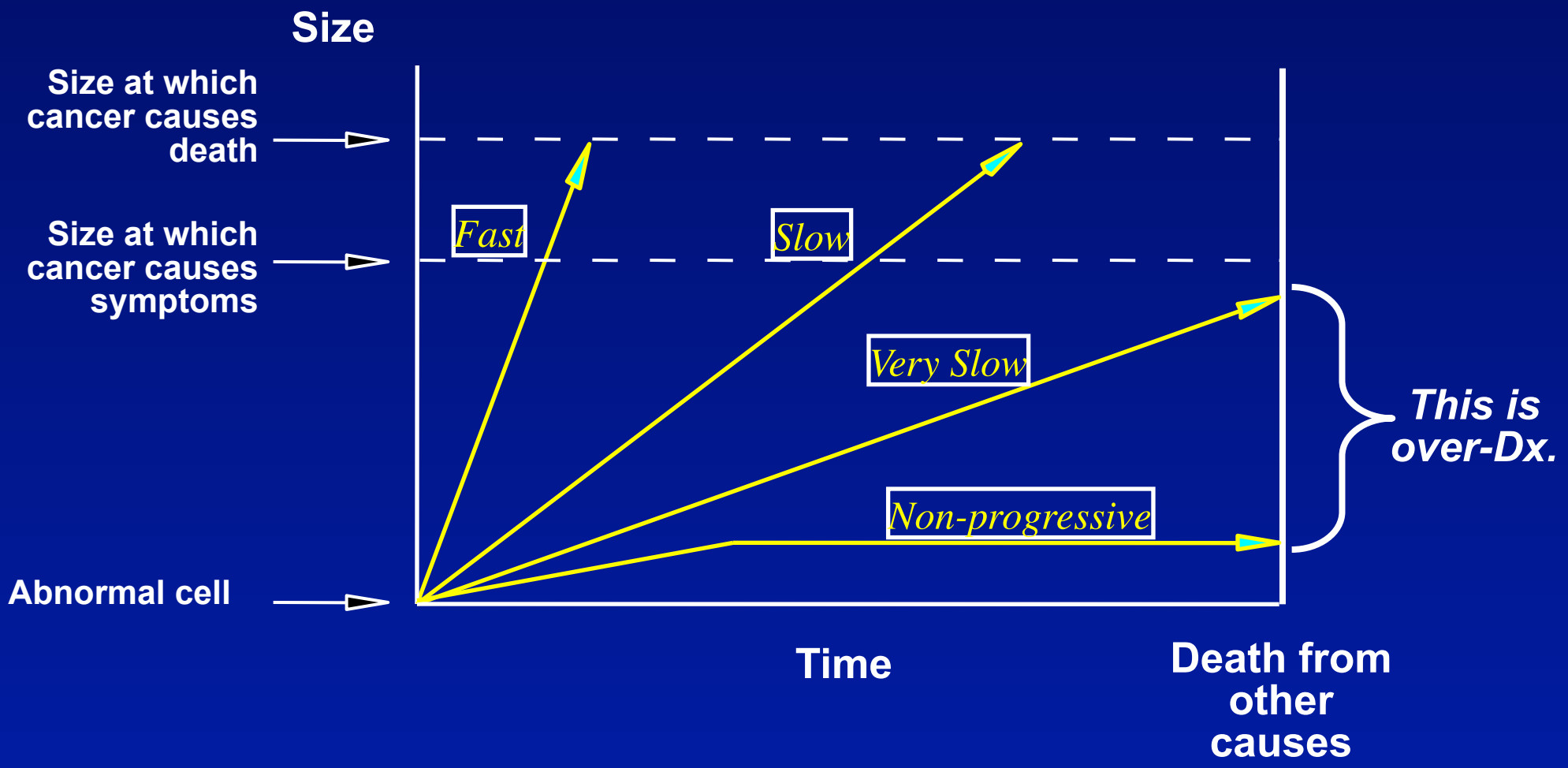


Requirements for Overdiagnosis

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)

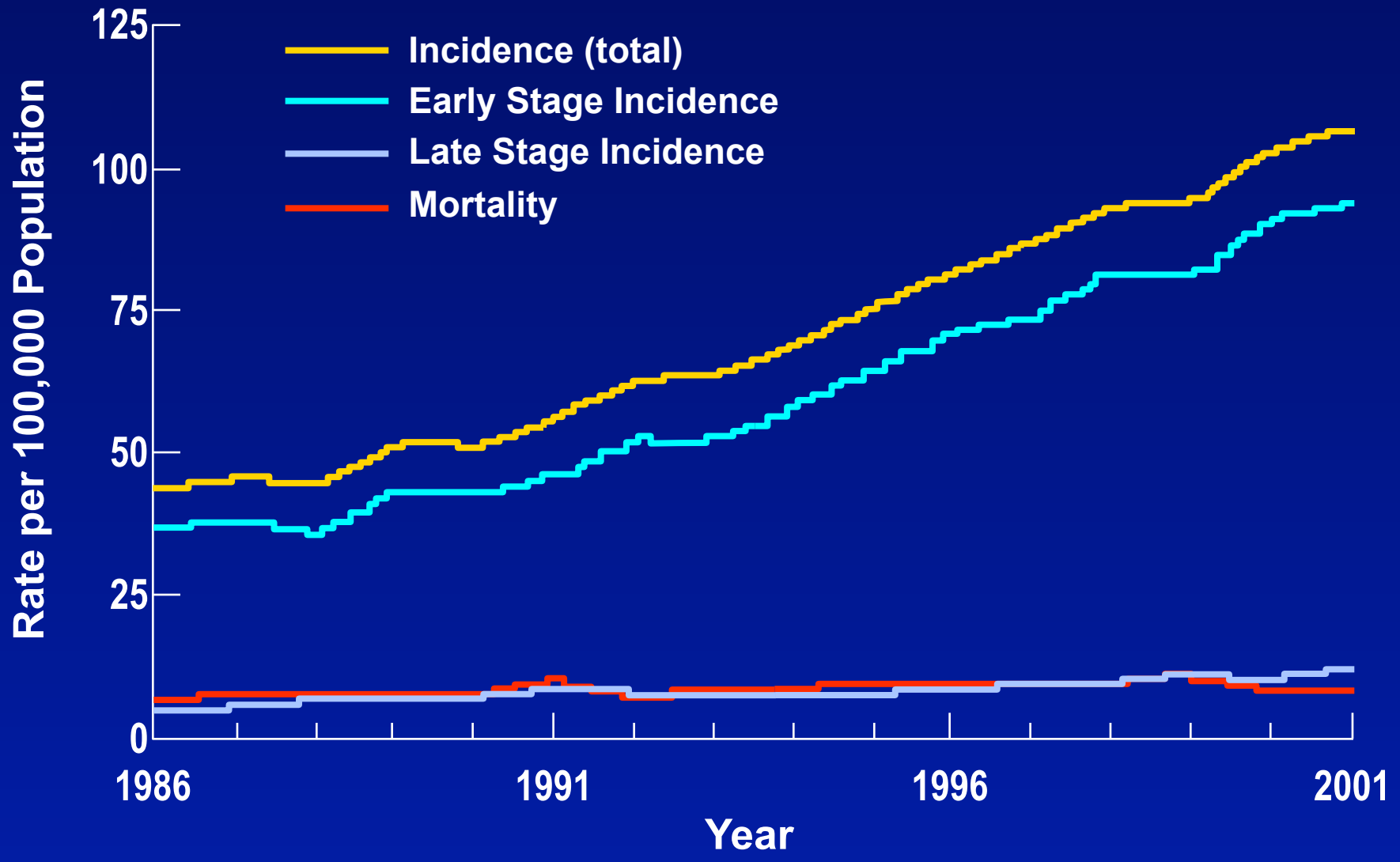
From G. Welch and W. Black, JNCI 2010

The Heterogeneity of Cancer Progression



(Courtesy of H. Gilbert Welch, Dartmouth)

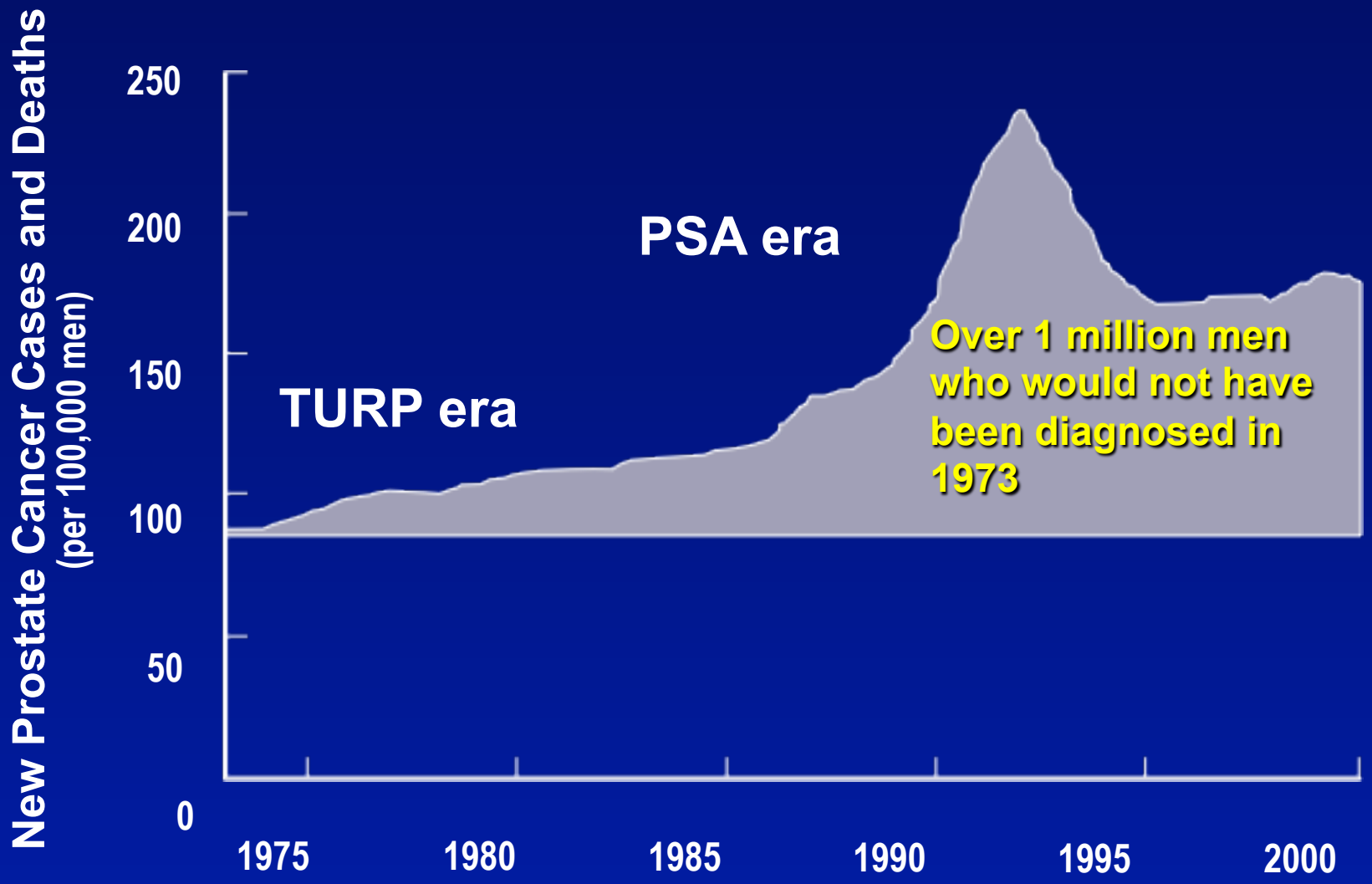
Evidence of Melanoma Overdiagnosis in the Medicare Population



G. Welch, *BMJ*, 2005

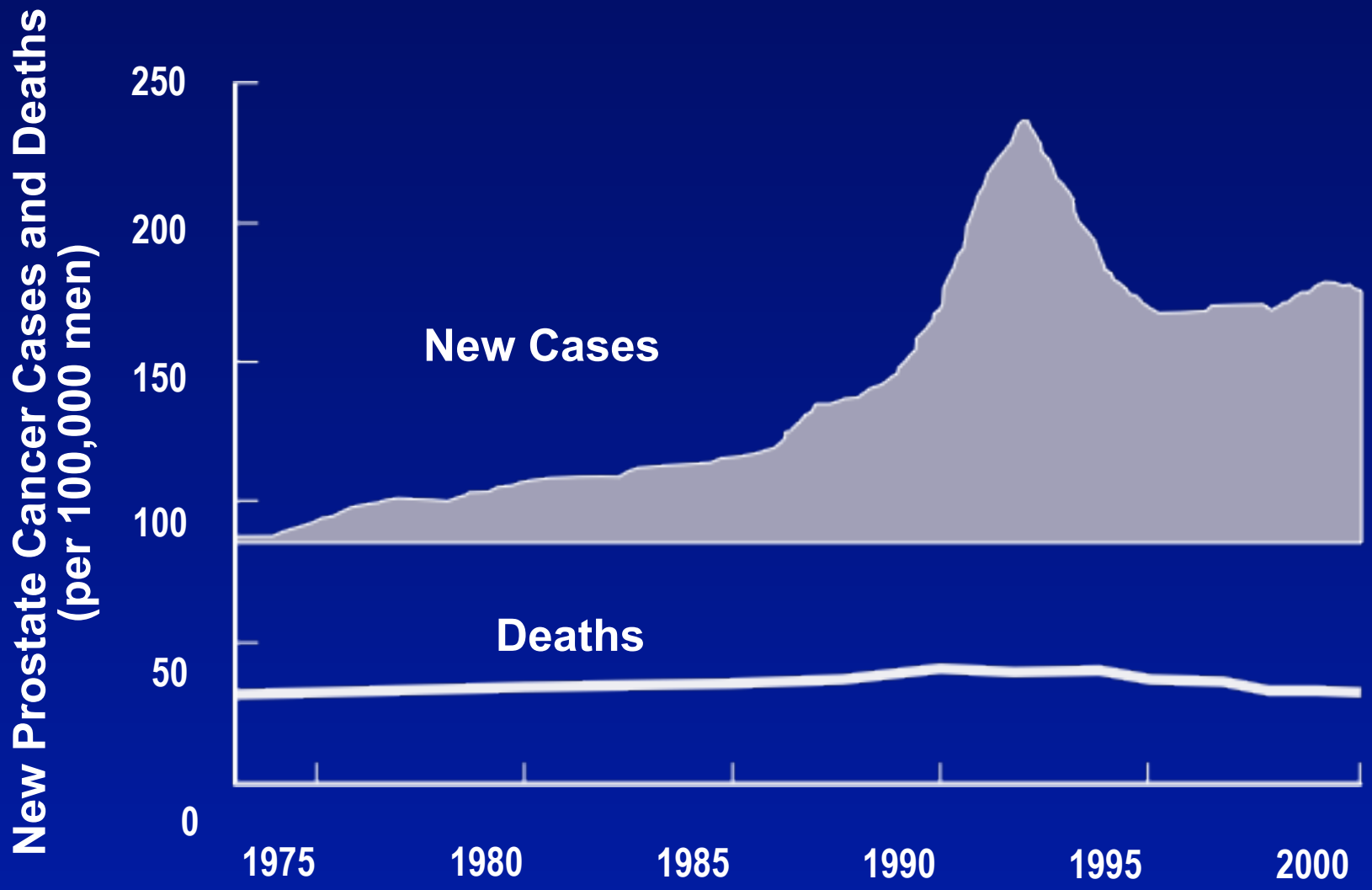
NCI Division of Cancer Prevention

The Prostate Cancer Pseudo-Epidemic in the U.S



(G. Welch, *"Should I Be Tested for Cancer?"*, 2004)

U.S. Prostate Cancer Incidence vs. Mortality Over-Diagnosis



From . Welch, *"Should I Be Tested for Cancer?"*, 2004

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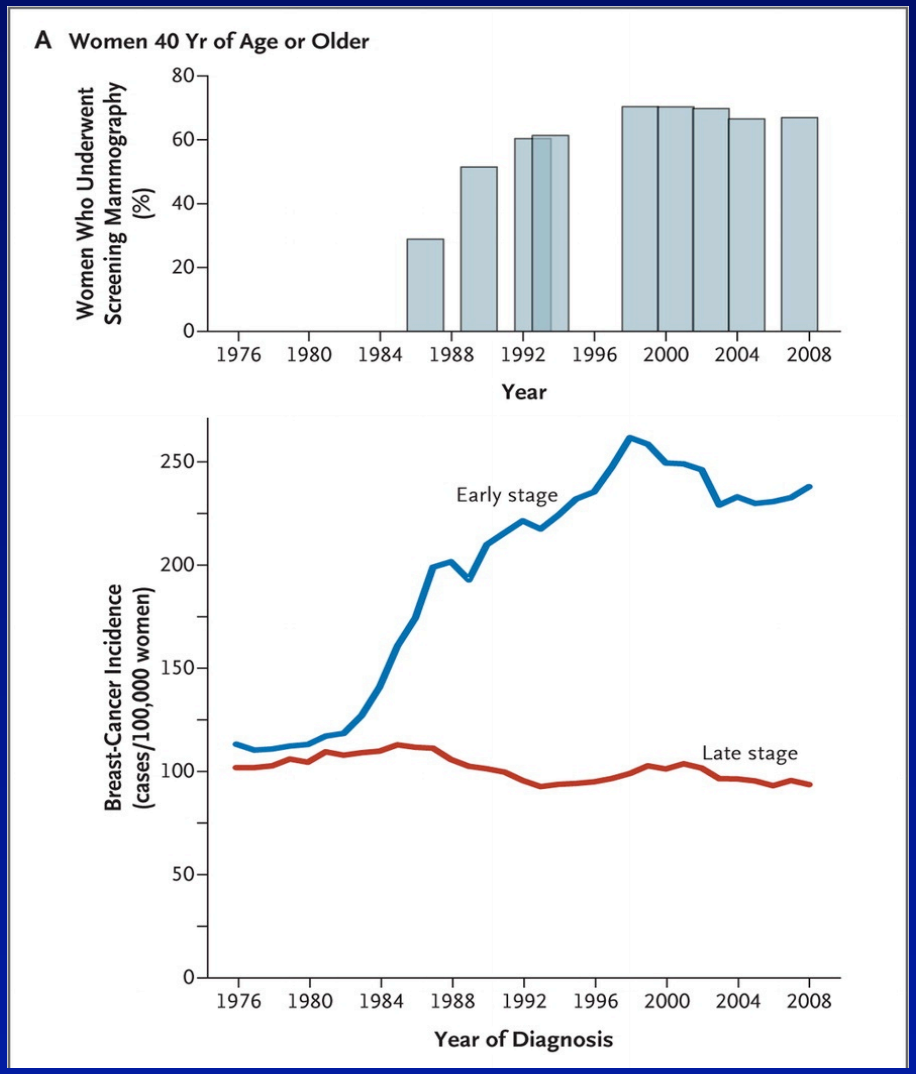
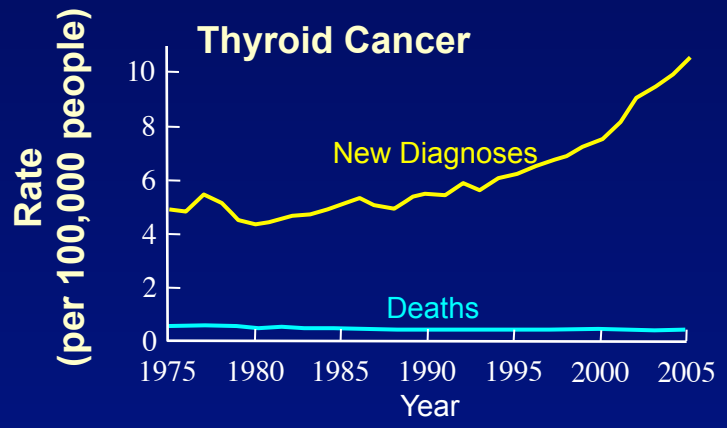
Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the U.S., 1976–2008

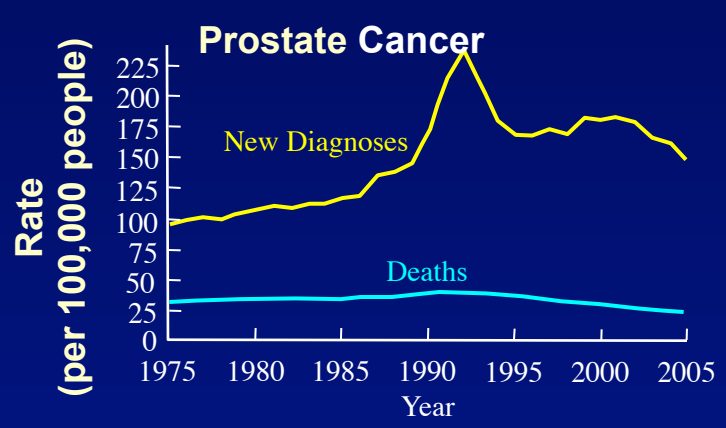


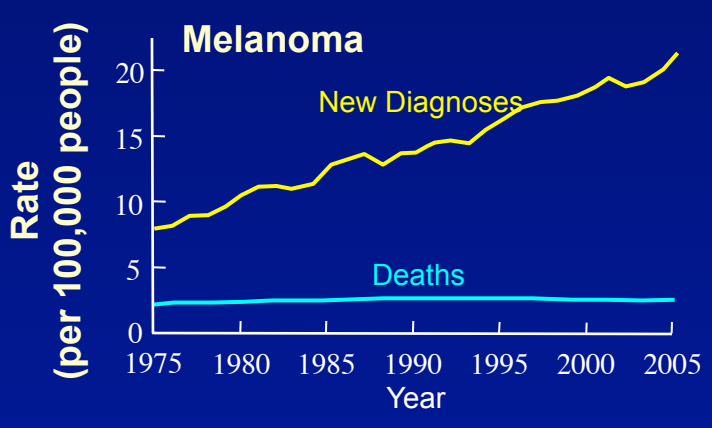
The NEW ENGLAND JOURNAL of MEDICINE

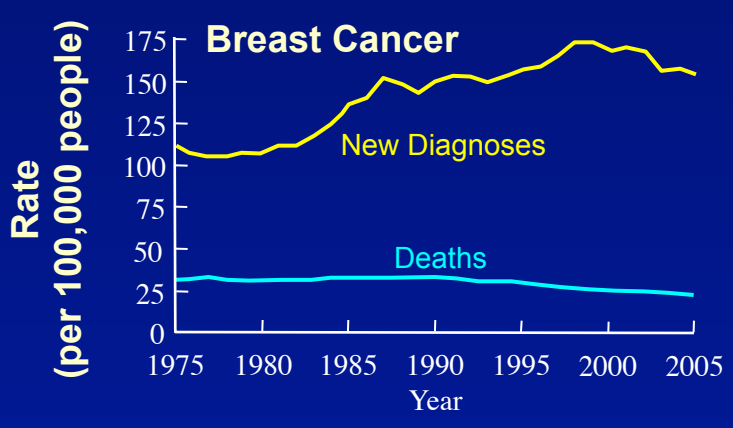
Bleyer A, Welch HG. N Engl J Med 2012;367:1998-2005.

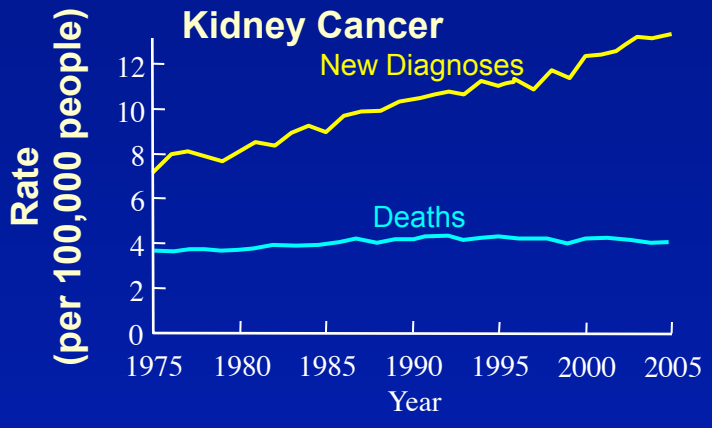
Incidence and Mortality of Five Cancers:
(Surveillance, Epidemiology, and End Results: SEER)











Source:
HG Welch, JNCI 2010

Current Challenge with Cancer Screening

Predicting whether lesions that are detected by sensitive screening tests are indolent (hence, not requiring immediate treatment) or progressive and potentially life-threatening

Strategies to Investigate Overdiagnosis

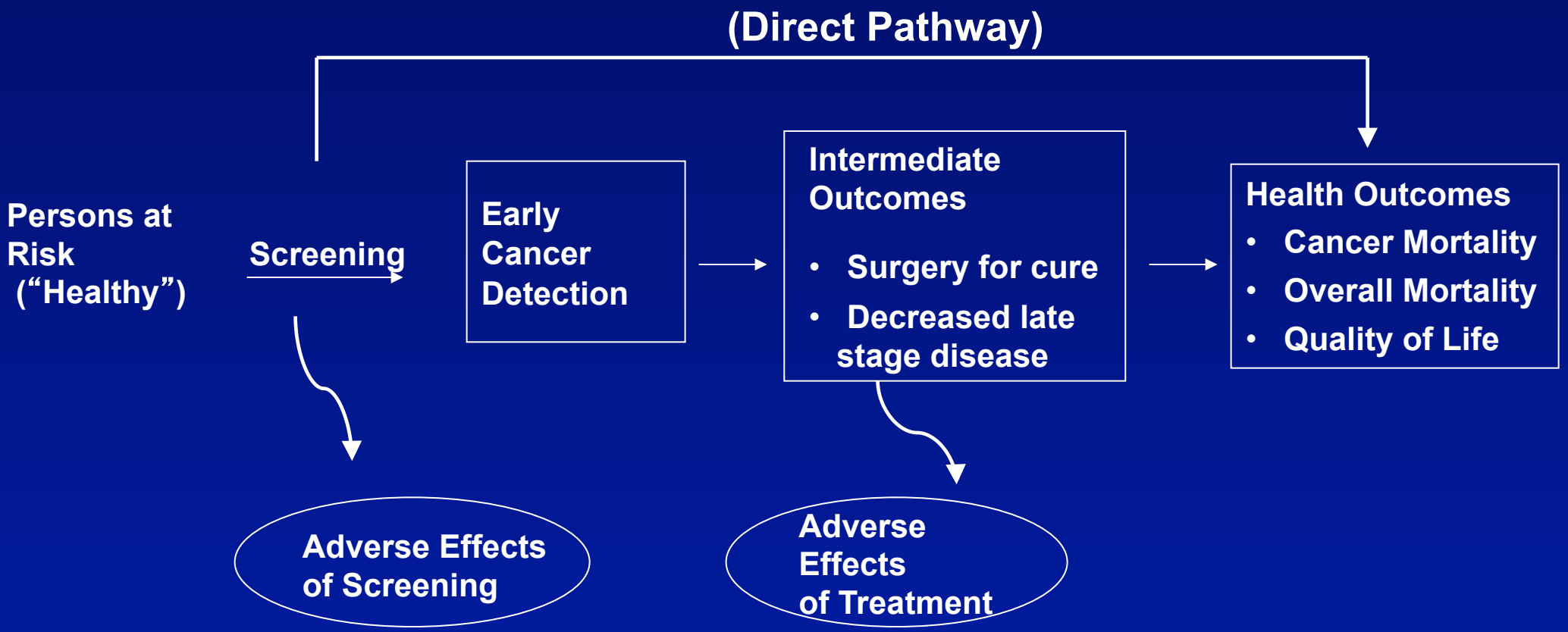
Annotate collected specimens with method of diagnosis

- Molecular patterns of screen-detected cases are enriched with overdiagnosed cases
- Molecular patterns of true interval cases are enriched with aggressive cases that we need to prevent (and target pathways for prevention)

Collect normal organ as well as the tumor

- Study cancer as a tissue-level, not simply a cell-based, disease
- Examples: prostate, breast, esophageal, melanoma

Analytic Framework for Cancer Screening



Consequences of Screening: The Good

1. Reduced risk of death from the target cancer (compared to no screening)
   - Nearly always need a randomized controlled trial to determine this
2. Reassurance (assuming healthy people need reassurance)

Consequences of Screening: The Bad

1. False reassurance when you have cancer
2. False alarms (false positive tests)
   - Harms of an unnecessary work-up
3. Harms of the test: bleeding, sepsis after biopsy, etc.
4. Detection of a lethal cancer without changing the outcome
   - Spend more of your life as a cancer patient
5. Detection of non-lethal cancers (over-diagnosis)
   - Unnecessary treatment
   - Treatment-related deaths of other causes (e.g., heart disease, secondary cancers)

How can we communicate the complexities of cancer screening to the public?

Study Findings: Low-dose CT versus Chest X-ray screening

53,454 current and former smokers were randomly assigned to be screened once a year for 3 years with low-dose CT or chest X-ray. Here's what happened after an average of 6.5 years:

	Low-dose CT 26,722 people		Chest X-ray 26,732 people
Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?			
4 in 1,000 fewer **died from lung cancer**	13 in 1,000	*versus*	17 in 1,000
5 in 1,000 fewer **died from all causes**	70 in 1,000	*versus*	75 in 1,000
Harm: What problems did CT scans cause compared to chest X-ray?			
223 in 1,000 more had at least one **false alarm**	365 in 1,000	*versus*	142 in 1,000
18 in 1,000 more had a **false alarm leading to an invasive procedure**, such as bronchoscopy, biopsy, or surgery	25 in 1,000	*versus*	7 in 1,000
2 in 1,000 more had a **major complication** from Invasive procedures	3 in 1,000	*versus*	1 in 1,000

Benefit-Harm Trade Off for a Decade of Annual Mammography Beginning at Age 50

For every 1,000 women aged 50

Benefit

0.3-3.2 Women will avoid dying from breast cancer

Harms

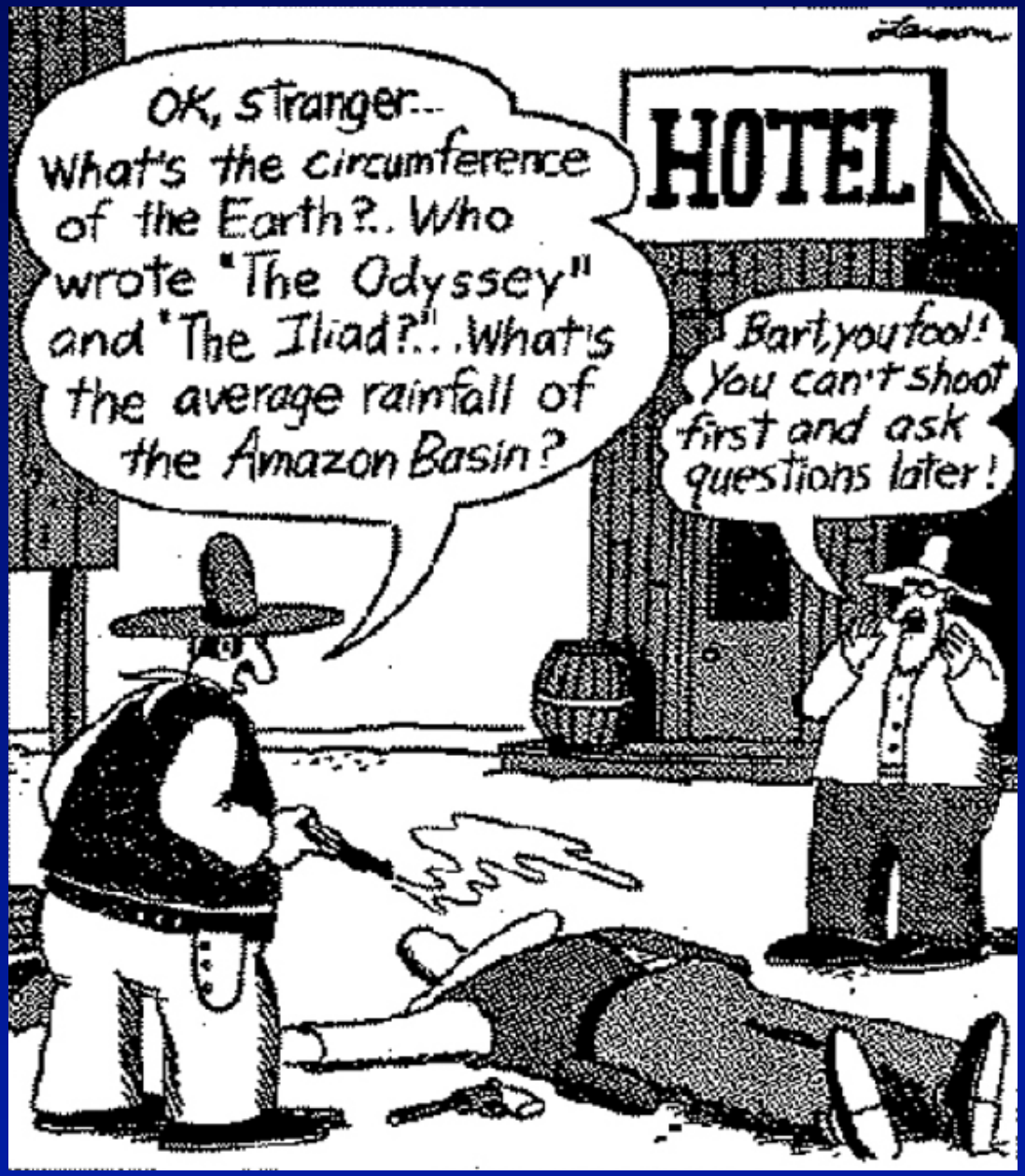
490-670 Women will have at least 1 “false alarm”

70-100 Women with a “false alarm” will undergo a biopsy

3-14 Women will be overdiagnosed and treated needlessly with surgery, radiation, and/or chemotherapy

Welch, *JAMA Internal Medicine*, Dec 2013

Are there lessons for the research and health professional community?


OK, stranger-- What's the circumference of the Earth?.. Who wrote "The Odyssey" and "The Iliad?".. What's the average rainfall of the Amazon Basin?
HOTEL
Bart, you fool! You can't shoot first and ask questions later!

Benefit-Harm Trade Off for a Decade of Annual Mammography Beginning at Age 40

For every 1,000 women aged 40

Benefit

0.1-1.6 Women will avoid dying from breast cancer

Harms

510-690 Women will have at least 1 “false alarm”

60-80 Women with a “false alarm” will undergo a biopsy

7-11 Women will be overdiagnosed and treated needlessly with surgery, radiation, and/or chemotherapy

Welch, *JAMA Internal Medicine*, Dec 2013

Benefit-Harm Trade Off for a Decade of Annual Mammography Beginning at Age 60

For every 1,000 women aged 60

Benefit

0.5-4.9 Women will avoid dying from breast cancer

Harms

390-540 Women will have at least 1 “false alarm”

50-70 Women with a “false alarm” will undergo a biopsy

6-20 Women will be overdiagnosed and treated needlessly with surgery, radiation, and/or chemotherapy

Welch, *JAMA Internal Medicine*, Dec 2013